REMARKS

Status of the Claims

Claims 1-20 are pending.

Rejection Under 35 U.S.C. § 103(a)

Reconsideration is respectfully requested of the rejection of claims 1-20 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,395,770 (Broder et al.) and US Application Pub. No. 2001/0029264 (McChesney-Harris) in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

Claim 1 is directed to a method of treating a patient afflicted with a cancer selected from the group consisting of breast, head, neck, esophageal, lung, and colon cancer by orally administering a pharmaceutical composition consisting essentially of a taxane, a solvent capable of dissolving the taxane, polyoxyethylatated castor oil, a diluent, and optionally a flavoring, wherein the taxane has a solubility in ethanol at room temperature of at least 200 mg/ml.

Broder et al. describe a method for making an orally administrable taxane bioavailable to human patients at a level sufficient to treat taxane-responsive conditions by orally co-administering a taxane and an oral bioavailability enhancing agent comprising a cyclosporin. All working examples of Broder et al. utilize paclitaxel as the taxane component.[1] While Broder et al. generally disclose that taxanes and derivatives thereof may be used, the specification emphasizes the use of paclitaxel.

Broder et al. do not disclose or quantify the solubility of taxanes in ethanol or suggest any benefit of utilizing a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml. Rather, Broder et al. disclose at length the preferential use of paclitaxel, a compound having a solubility in ethanol of less than

[1] Broder et al., U.S. Pat. No. 6,395,770, Examples 1-4.

40 mg/ml.[2] Instead of addressing the solubility of different taxanes, Broder et al. emphasize that absorption/bioavailability of a taxane may be increased by coadministering a cyclosporin compound rather than select a taxane having a property of increased solubility in ethanol. Thus, one skilled in the art would not be motivated by Broder et al. to identify and select a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml for a method of treating cancer.

McChesney-Harris describes compositions for treating taxane-responsive conditions comprising paclitaxel and other taxanes or their water insoluble derivatives, Vitamin E-TPGS, and an organic solvent.[3] The disclosed compositions are designed to overcome solubility problems of taxanes while avoiding toxicity problems of CHREMOPHOR® EL which the prior art used to solubilize water insoluble taxanes.[4]

While McChesney-Harris generally discloses a taxane composition for treating a taxane-responsive conditions, paclitaxel is the only taxane which is specifically disclosed. Furthermore, McChesney-Harris discloses that attempting to increase paclitaxel's solubility by **altering its chemical structure can potentially decrease the antitumor activity of the drugs and does not address the problem of low stability and short shelf life.**[5] Thus, McChesney-Harris emphasizes a composition wherein a taxane is made soluble by mixing the taxane with d-alpha-tocopheryl polyethylene glycol 100 succinate (Vitamin E-TPGS) and an organic solvent rather than altering its chemical structure or selecting a taxane having a specified solubility in ethanol.[6]

Goodman and Gillman disclose that paclitaxel has very limited solubility and must be administered in a vehicle of 50% ethanol and 50% polyethoxyethylated castor

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[2] *TAXOL Science and Applications*, Edited by Matthew Suffness, CRC Press, ISBN0-8493-8382-X, Chapter 9 Biopharmaceutics of paclitaxel (taxol): Formulation, activity, and pharmacokinetics, page 238, written by Robert Straubinger

[3] McChesney-Harris, U.S. Pub. No. 2001/0029264, paragraphs [0009] and [0012].

[4] *Id.*, paragraph [0006].

[5] *Id.*, paragraph [0007].

[6] *Id.*, paragraph [0012].

oil. Goodman and Gillman do not address oral administration of taxanes; rather, they only discuss the administration of paclitaxel in the form of infusions.

Prima Facie Obviousness Not Established

For a claim to be *prima facie* obvious under 35 U.S.C. §103 in view of prior art, the prior art references must individually or in combination disclose or suggest all of the limitations of the claim. The references must also suggest or provide a motivation to one skilled in the art to modify the cited references or combine their teachings. Finally, one skilled in the art, upon reading the prior art references, must have a reasonable expectation of success in modifying or combining the references.[7]

No Reasonable Expectation of Success

McChesney-Harris discloses that prior art attempts to improve the solubility of paclitaxel were unsuccessful. Specifically, McChesney-Harris states:

> "Extensive efforts have been made to circumvent [water solubility] problems inherent in the administration of paclitaxel. For example, in U.S. Pat. No. 4,942,184, Haugwitz et al. attempted to make paclitaxel more water soluble by altering its chemical structure. See also U.S. Pat. No. 4,960,790. This changing of the chemical structure of paclitaxel can potentially decrease the antitumor activity of the drugs, and does not address the problem of low stability and short shelf life."[8] *Emphasis added.*

Thus, McChesney-Harris discloses evidence that due to the failures in the prior art, one skilled in the art would not have had a reasonable expectation of success, but would have rather had an expectation of failure in improving the solubility of a taxane.

All Elements of Claim 1 are not Disclosed in Cited References

The Office asserts that it would be obvious or inherent that the disclosed taxanes and water soluble derivatives would exhibit the claimed solubility. None of the cited

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[7] MPEP §§ 2143-2143.03.

[8] *McChesney-Harris*, U.S. Application Publication No. 2001/0029264A1, paragraph [0007].

references, however, disclose or suggest a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml. Furthermore, none of the references suggest that any advantage could be derived by selecting a taxane having a solubility in ethanol which is greater than that of paclitaxel. Thus, without more, selection of a taxane having a solubility in ethanol at room temperature of at least 200 mg/ml is not disclosed or suggested. Moreover, the general disclosure of the chemical group of taxanes without more does not render the claimed element obvious merely because a claimed element may be inherent in some compounds of the disclosed genus:

> [T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.[9]

Thus, an undisclosed taxane having an unrecognized advantage of a solubility in ethanol at room temperature of at least 200 mg/ml cannot support an obviousness rejection of claim 1.

No Motivation is Disclosed or Suggested to Combine Elements of Claim 1

The cited references fail to disclose or suggest a motivation to combine all the elements of claim 1. As discussed above, none of the cited references disclose a taxane that has a solubility in ethanol at room temperature of at least 200 mg/ml or the desirability of such a solubility in ethanol. The references, at most, disclose that taxane insolubility in water is an obstacle to absorption or bioavailability, which is not equivalent. Both Broder and McChesney-Harris disclose compositions to improve absorption and/or water solubility of taxane wherein a second compound is used to increase the bioavailability or water solubility of taxane (e.g. Broder et al.'s use of cyclosporin and McChesney-Harris's use of Vitamin E-TPGS). Thus, the Office has not articulated how the prior art provides a motivation to combine the elements of claim 1.

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[9] *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A 1977)(quoting *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966)). *See also In re Naylor*, 369 F.2d 765, 768, 152 U.S.P.Q. 106, 108 (C.C.P.A. 1966) ("[Inherency] is quite immaterial if . . . one of ordinary skill in the art would not appreciate or recognize that inherent result."); *In re Rijckaert*, 9 F.3d 1531, 1533, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).

Instead of providing a motivation to combine teachings, McChesney-Harris teaches away from modifying taxane compounds to increase their solubility in water by disclosing that attempts to change the "chemical structure of paclitaxel can potentially decrease the antitumor activity of the drugs, and does not address the problem of low stability and short shelf life."[10] Thus, contrary to the Office's assertion, one skilled in the art reading McChesney-Harris or the prior art therein would be led away from modifying taxane compounds to increase their solubility.

The Office vaguely asserts that one skilled in the art would be motivated by a reasonable expectation of success to modify the compositions disclosed by Broder et al. and McChesney-Harris such that the taxane would be sufficiently soluble to be therapeutically effective. However, a "reasonable expectation of success" by itself is not a valid source of motivation. Rather, "[t]here are three possible sources for a motivation to combine references: The nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art."[11]

The Office appears to be utilizing impermissible hindsight reconstruction by essentially asserting that since the applicants have successfully described the method of claim 1, one skilled in the art would likewise be motivated by an expectation of success to modify the compositions of disclosed by Broder et al. and McChesney-Harris, which do not disclose all the claimed elements, to derive the claimed method with all its elements. Without using impermissible hindsight reconstruction, however, one skilled in the art would not have any reasonable expectation of success. The Office has not, and cannot, point to any disclosure or suggestion in the art, other than the Applicant's, which provides such an expectation.

The Initial Burden of Proof to Factually Support Obviousness Rejections is Unmet

The Office has failed to meet its initial burden of providing factual support for its obviousness rejections. The Office asserts that since Broder and McChesney-Harris

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[10] *McChesney-Harris*, U.S. Application Publication No. 2001/0029264A1, paragraph [0007].

[11] *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998); MPEP § 2143.01.

generally disclose the use of taxanes, such taxanes would, "absent evidence to the contrary, . . . obviously, if not inherently, exhibit the claimed solubility in ethanol."[12] The Office further asserts that "[a]bsent evidence to the contrary," one skilled in the art would be motivated by an expectation of success to modify the compositions such that the taxane was sufficiently soluble to be therapeutically effective.[13]

The concept of *prima facie* obviousness allocates the burden of producing evidence during the examination process. "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness."[14] However, the Office repeatedly asserts the claims are obvious "absent evidence to the contrary," without providing specific factual support of the assertion. By doing so, the Office is improperly attempting to shift the burden of proof to the applicant without first meeting its burden of factually supporting any *prima facie* conclusion of why the claimed invention is unpatentable. The phrase "absent evidence to the contrary," instead of supporting an obviousness rejection, indicates that the Office cannot find prior art necessary to factually support their improper conclusion of obviousness. It is the Office's obligation, not the Applicant's, to provide evidence that factually supports an obviousness rejection. Absent such evidence, no shift of burden occurs, and the applicant is under no obligation to submit evidence of non-obviousness.[15]

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[12] Office action, page 4, paragraph 2, emphasis added.

[13] Office action, page 5, paragraph 1, emphasis added.

[14] MPEP § 2142, emphasis added.

[15] MPEP § 2142.

CONCLUSION

The Office has failed to cite prior art which individually or in combination discloses all that claim 1 requires and has failed to identify where the prior art suggests or provides a motivation to one skilled in the art to modify or combine the teachings of the cited references. Therefore, one skilled in the art reading the cited references could not have a reasonable expectation of success in modifying or combining the references to obtain the method of claim 1. The Office has therefore failed to meet its burden of supporting its *prima facie* conclusion of obviousness for claim 1. Claims 2-20 include the requirements of claim 1 and are patentable for the same reasons as those set forth for claim 1 and by reason of the further requirements which they specify.

In light of the foregoing, the applicants respectfully request withdrawal of the rejection of claims 1-20 under 35 U.S.C. §103(a).

The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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